

IN THE CLAIMS:

Please substitute original claims numbered 8, 9, 23, 24, 25, 26, 28, 43, 44, 47, 56, 57, 58, 59, and 61 with the following amended claims having the same claim numbers.

Please cancel claim numbers 11, 12, 13, 14, 27, 29, 30, 46, 48, 49, 60, 62 and 63 without prejudice or disclaimer.

Please add for consideration new claim numbers 67-70.

1. (withdrawn) A therapeutic method of treating age associated memory impairment (AAMI), mild cognitive impairment (MCI), cerebrovascular dementia (CVD) and related retrogenic degenerative neurological conditions, comprising administering a therapeutically effective amount of at least one agent capable of inhibiting a neuronal cell cycle progression.
2. (withdrawn) The therapeutic method of claim 1, wherein the at least one agent is capable of inhibiting neuronal cell cycle progression before entry of a neuronal cell into a synthesis (S) phase.
3. (withdrawn) The therapeutic method of claim 1, wherein the at least one agent is capable of inhibiting neuronal cell cycle progression at or prior to the early growth (G₁) phase.
4. (withdrawn) The therapeutic method of claim 1, wherein the at least one agent is selected from the group consisting of minocycline, any tetracycline family derivative capable of crossing the blood brain barrier, acetylsalicylic acid, any salicylate which inhibits early phase cell cycle progression, sirolimus, any sirolimus derivative capable of inhibiting early cell cycle progression, flavopiridol, ciclopirox, a paulone, indirubin, faspaplycin, olomoucine, roscovitine, Aragusterol A, valproate, N-(3-chloro-7-indolyl)-

1,4-benzenedisulfamide, a farnesyl transferase inhibitor such as R115777, SCH66336 and BMS-214662, and sodium butyrate.

5. (withdrawn) A method of treating age associated memory impairment (AAMI), mild cognitive impairment (MCI), cerebrovascular dementia (CVD) and related retrogenic degenerative neurological conditions, comprising administering a therapeutically effective amount of (i) at least one first agent capable of inhibiting neuronal cell cycle division before entry of a neuronal cell into an early phase of said cell cycle, and optionally (ii) at least one second agent capable of inhibiting cell cycle progression at any one or more of the phases of the cell cycle.

6. (withdrawn) The method of claim 5, wherein the at least one first agent is selected from the group consisting of minocycline, any tetracycline family derivative capable of crossing the blood brain barrier, acetylsalicylic acid, any salicylate which inhibits early phase cell cycle progression, sirolimus, any sirolimus derivative capable of inhibiting early cell cycle progression, a paulone, indirubin, fascaplycin, olomoucine, roscovitine, Aragusterol A, valproate, N-(3-chloro-7-indolyl)-1,4-benzenedisulfamide, a farnesyl transferase inhibitor such as R115777, SCH66336 and BMS-214662, and sodium butyrate.

7. (withdrawn) The method of claim 5, wherein the at least one second agent is selected from the group consisting of flavopiridol, ciclopirox, and methotrexate.

8. (currently amended) A method of treating age associated memory impairment (AAMI), mild cognitive impairment (MCI), cerebrovascular dementia (CVD) and related retrogenic ~~degenerative neurological conditions~~ diseases, comprising administering a therapeutically effective amount of:

i) at least one first agent capable of inhibiting neuronal cell cycle progression ~~at or before an early phase~~;

ii) at least one second agent capable of inhibiting ~~neuronal cell cycle progression generally; and optionally~~ activated microglial-induced mitogenic stimulation, wherein the

at least one second agent is an anti-inflammatory agent selected from the group consisting of a non-steroidal anti-inflammatory agent (NSAIDS), a salicylate, a steroid and an immunophillin; and

iii) at least one third agent capable of inhibiting ~~mitogenic stimulation~~ glutamate-induced cytotoxicity, wherein the at least one third agent is selected from the group consisting of memantine, neramexane, amantadine, riluzole, MK801, ketamine, dextromethorphan, dextrorphan, phencyclidine, and dexanabinol (HU-211).

9. (currently amended) The method of claim 8 wherein the first agent is selected from the group consisting of minocycline, any tetracycline ~~family derivative~~ capable of crossing the blood brain barrier, acetylsalicylic acid, any salicylate which inhibits ~~early phase~~ cell cycle progression, sirolimus, any sirolimus ~~derivative~~ capable of ~~inhibiting early~~ inhibiting cell cycle progression, a paulone, indirubin, faspaplycin, olomoucine, roscovitine, Aragusterol A, valproate, N-(3-chloro-7-indolyl)-1,4-benzenedisulfamide, a farnesyl transferase inhibitor such as R115777, SCH66336 and BMS-214662, and sodium butyrate.

10. (withdrawn) The method of claim 8, wherein the second agent is selected from the group consisting of flavopiridol, ciclopirox, and methotrexate.

11. (canceled)

12. (canceled)

13. (canceled)

14. (canceled)

15. (withdrawn) The method of claim 14, wherein the NSAID is selected from the group consisting of ibuprofen, naproxen, celecoxib, rofecoxib, sulindac, piroxicam,

indomethacin, etodolac, nabumetone, tolmetin, diclofenac, ketoprofen, apazone, and meloxicam.

16. (withdrawn) The method of claim 14, wherein the steroid is a glucocorticoid.

17. (withdrawn) The method of claim 16, wherein the glucocorticoid is prednisone.

18. (withdrawn) The method of claim 14, wherein the immunophilins is selected from the group consisting of cyclosporine A and tacrolimus.

19. (withdrawn) The method of claim 5, wherein the first agent is capable of inhibiting neuronal cell cycle progression at, or prior to entry into, the early growth (G_1) phase.

20. (withdrawn) The method of claim 5, wherein the first agent is capable of inhibiting neuronal cell cycle progression at, or prior to entry into, the synthesis (S) phase.

21. (withdrawn) The method of claim 20, wherein the agent is selected from the group consisting of minocycline, any tetracycline family derivative capable of crossing the blood brain barrier, acetylsalicylic acid, any salicylate which inhibits early phase cell cycle response, sirolimus, any sirolimus derivative capable of inhibiting early cell cycle progression, a paclitaxel, indirubin, fascaplycin, olomoucine, roscovitine, Aragusterol A, valproate, N-(3-chloro-7-indolyl)-1,4-benzenedisulfamide, a farnesyl transferase inhibitor such as R115777, SCH66336 and BMS-214662, and sodium butyrate.

22. (withdrawn) The method of claim 1, wherein the subject is a human.

23. (currently amended) A method of treating age associated memory impairment (AAMI), mild cognitive impairment (MCI), or cerebrovascular dementia (CVD), in a subject with AAMI, MCI, or CVD, comprising administering a therapeutically effective amount of (i) at least one first agent capable of inhibiting neuronal cell cycle progression, ~~and~~ (ii) at least one second agent capable of reducing mitogenic stimulation, wherein the

at least one second agent is an anti-inflammatory agent selected from the group consisting of a non-steroidal anti-inflammatory agent (NSAIDS), a salicylate, a steroid and an immunophilin; and iii) at least one third agent capable of inhibiting glutamate-induced cytotoxicity.

24. (currently amended) The method of claim 23, wherein the at least one first agent inhibits cell cycle progression prior to entry of a neuronal cell into a synthesis (S) phase ~~and the at least one second agent is capable of inhibiting glutamate-induced excitotoxicity and/or reducing activated microglia-induced mitogenic stimulation.~~

25. (currently amended) The method of claim 23, wherein the at least one first agent inhibits cell cycle progression at or prior to entry of a neuronal cell into, an early growth (G₁) phase ~~and the at least one second agent is capable of inhibiting glutamate-induced excitotoxicity and/or reducing activated microglia-induced mitogenic stimulation.~~

26. (currently amended) The therapeutic method of claim 23, wherein the at least one first agent is selected from the group consisting of minocycline, any tetracycline family derivative capable of crossing the blood brain barrier, acetylsalicylic acid, any salicylate which inhibits ~~early phase~~ cell cycle progression, sirolimus, any sirolimus derivative capable of inhibiting ~~early~~ cell cycle progression, a paclitaxel, indirubin, fasaplycin, olomoucine, roscovitine, Aragusterol A, valproate, N-(3-chloro-7-indolyl)-1,4-benzenedisulfamide, a farnesyl transferase inhibitor such as R115777, SCH66336 and BMS-214662, and sodium butyrate.

27. (canceled)

28. (currently amended) The method of claim ~~27~~ 23, wherein the inhibitor of glutamate-induced excitotoxicity is selected from the group consisting of memantine, neramexane, amantadine, riluzole, MK801, ketamine, dextromethorphan, dextrorphan, phencyclidine, and dexanabinol (HU-211).

29. (canceled)

30. (canceled)

31. (withdrawn) The method of claim 30, wherein the NSAID is selected from the group consisting of ibuprofen, naproxen, celecoxib, rofecoxib, sulindac, piroxicam, indomethacin, etodolac, nabumetone, tolmetin, diclofenac, ketoprofen, apazone, and meloxicam.

32. (withdrawn) The method of claim 30, wherein the steroid is a glucocorticoid.

33. (withdrawn) The method of claim 32, wherein the glucocorticoid is prednisone.

34. (withdrawn) The method of claim 30, wherein the immunophillin is selected from the group consisting of cyclosporine A and tacrolimus.

35. (withdrawn) The method of claim 23 wherein the at least one first agent is selected from the group consisting of flavopiridol, ciclopirox, and methotrexate and the at least one second agent acts to inhibit glutamate-induced excitotoxicity and/or activated microglia-induced mitogenic stimulation.

36. (withdrawn) A therapeutic method of treating age associated memory impairment (AAMI), mild cognitive impairment (MCI), Alzheimer's disease (AD), cerebrovascular dementia (CVD) and related retrogenic degenerative neurological conditions, comprising administering a therapeutically effective amount of at least one agent capable of inhibiting a neuronal cell cycle progression.

37. (withdrawn) The therapeutic method of claim 36, wherein the at least one agent is capable of inhibiting neuronal cell cycle progression before entry of a neuronal cell into a synthesis (S) phase.

38. (withdrawn) The therapeutic method of claim 36, wherein the at least one agent is capable of inhibiting neuronal cell cycle progression at or prior to the early growth (G₁) phase.

39. (withdrawn) The therapeutic method of claim 36, wherein the at least one agent is selected from the group consisting of minocycline, any tetracycline family derivative capable of crossing the blood brain barrier, acetylsalicylic acid, any salicylate which inhibits early phase cell cycle progression, flavopiridol, ciclopirox, a paulone, indirubin, olomoucine, roscovitine, Aragusterol A, N-(3-chloro-7-indolyl)-1,4-benzenedisulfamide, and a farnesyl transferase inhibitor such as R115777, SCH66336 or BMS-214662.

40. (withdrawn) A method of treating age associated memory impairment (AAMI), mild cognitive impairment (MCI), Alzheimer's disease (AD), cerebrovascular dementia (CVD) and related retrogenic degenerative neurological conditions, comprising administering a therapeutically effective amount of (i) at least one first agent capable of inhibiting neuronal cell cycle division before entry of a neuronal cell into an early phase of said cell cycle, and optionally (ii) at least one second agent capable of inhibiting cell cycle progression at any one or more of the phases of the cell cycle.

41. (withdrawn) The method of claim 40, wherein the at least one first agent is selected from the group consisting of minocycline, any tetracycline family derivative capable of crossing the blood brain barrier, acetylsalicylic acid, any salicylate which inhibits early phase cell cycle progression, a paulone, indirubin, olomoucine, roscovitine, Aragusterol A, N-(3-chloro-7-indolyl)-1,4-benzenedisulfamide, and a farnesyl transferase inhibitor such as R115777, SCH66336 or BMS-214662.

42. (withdrawn) The method of claim 40, wherein the at least one second agent is selected from the group consisting of flavopiridol, ciclopirox, and methotrexate.

43. (currently amended) A method of treating age associated memory impairment (AAMI), mild cognitive impairment (MCI), Alzheimer's disease (AD), cerebrovascular

dementia (CVD) and related retrogenic ~~degenerative neurological conditions~~ diseases, comprising administering a therapeutically effective amount of:

i) at least one first agent capable of inhibiting neuronal cell cycle progression ~~at or before an early phase~~;

ii) at least one second agent capable of inhibiting ~~neuronal cell cycle progression generally; and optionally~~ activated microglial-induced mitogenic stimulation, wherein the at least one second agent is an anti-inflammatory agent selected from the group consisting of a non-steroidal anti-inflammatory agent (NSAIDS), a salicylate, a steroid and an immunophillin; and

iii) at least one third agent capable of inhibiting ~~mitogenic stimulation~~ glutamate-induced cytotoxicity.

44. (currently amended) The method of claim 43 wherein the first agent is selected from the group consisting of minocycline, any tetracycline ~~family derivative~~ capable of crossing the blood brain barrier, acetylsalicylic acid, any salicylate which inhibits ~~early phase~~ cell cycle progression, a paulone, indirubin, olomoucine, roscovitine, Aragusterol A, N-(3-chloro-7-indolyl)-1,4-benzenedisulfamide, and a farnesyl transferase inhibitor such as R115777, SCH66336 or BMS-214662.

45. (withdrawn) The method of claim 43, wherein the second agent is selected from the group consisting of flavopiridol, ciclopirox, and methotrexate.

46. (canceled)

47. (currently amended) The method of claim ~~46~~ 43, wherein the ~~inhibitor of third agent~~ capable of inhibiting glutamate-induced excitotoxicity is selected from the group consisting of memantine, neramexane, amantadine, riluzole, MK801, ketamine, dextromethorphan, dextrophan, phencyclidine, and dexanabinol (HU-211).

48. (canceled)

49. (canceled)

50. (withdrawn) The method of claim 49, wherein the NSAID is selected from the group consisting of ibuprofen, naproxen, celecoxib, rofecoxib, sulindac, piroxicam, indomethacin, etodolac, nabumetone, tolmetin, diclofenac, ketoprofen, apazone, and meloxicam.

51. (withdrawn) The method of claim 49, wherein the immunophillin is cyclosporine A.

52. (withdrawn) The method of claim 40, wherein the first agent is capable of inhibiting neuronal cell cycle progression at, or prior to entry into, the early growth (G₁) phase.

53. (withdrawn) The method of claim 40, wherein the first agent is capable of inhibiting neuronal cell cycle progression at, or prior to entry into, the synthesis (S) phase.

54. (withdrawn) The method of claim 53, wherein the agent is selected from the group consisting of minocycline, any tetracycline family derivative capable of crossing the blood brain barrier, acetylsalicylic acid, any salicylate which inhibits early phase cell cycle response, a paclitaxel, indirubin, olomoucine, roscovitine, Aragusterol A, N-(3-chloro-7-indolyl)-1,4-benzenedisulfamide, and a farnesyl transferase inhibitor such as R115777, SCH66336 or BMS-214662.

55. (withdrawn) The method of claim 36, wherein the subject is a human.

56. (currently amended) A method of treating age associated memory impairment (AAMI), mild cognitive impairment (MCI), Alzheimer's disease (AD), or cerebrovascular dementia (CVD), in a subject with AAMI, MCI, AD, or CVD, comprising administering a therapeutically effective amount of (i) at least one first agent capable of inhibiting neuronal cell cycle progression, and (ii) at least one second agent capable of reducing mitogenic stimulation wherein the at least one second agent is an anti-inflammatory agent selected from the group consisting of a non-steroidal anti-

inflammatory agent (NSAID), a salicylate, a steroid and an immunophillin; and iii) at least one third agent capable of inhibiting glutamate-induced cytotoxicity.

57. (currently amended) The method of claim 56, wherein the at least one first agent inhibits cell cycle progression prior to entry of a neuronal cell into a synthesis (S) phase ~~and the at least one second agent is capable of inhibiting glutamate-induced excitotoxicity and/or reducing activated microglia-induced mitogenic stimulation.~~

58. (currently amended) The method of claim 56, wherein the at least one first agent inhibits cell cycle progression at or prior to entry of a neuronal cell into, an early growth (G₁) phase ~~and the at least one second agent is capable of inhibiting glutamate-induced excitotoxicity and/or reducing activated microglia-induced mitogenic stimulation.~~

59. (currently amended) The therapeutic method of claim 56, wherein the at least one first agent is selected from the group consisting of minocycline, any tetracycline ~~family derivative~~ capable of crossing the blood brain barrier, acetylsalicylic acid, any salicylate which inhibits ~~early phase~~ cell cycle progression, a paulone, indirubin, olomoucine, roscovitine, Aragusterol A, N-(3-chloro-7-indolyl)-1,4-benzenedisulfamide, and a farnesyl transferase inhibitor such as R115777, SCH66336 or BMS-214662.

60. (canceled)

61. (currently amended) The method of claim ~~60~~ 56, wherein the inhibitor of glutamate-induced excitotoxicity is selected from the group consisting of memantine, neramexane, amantadine, riluzole, MK801, ketamine, dextromethorphan, dextrorphan, phencyclidine, and dexanabinol (HU-211).

62. (canceled)

63. (canceled)

64. (withdrawn) The method of claim 62, wherein the NSAID is selected from the group consisting of ibuprofen, naproxen, celecoxib, rofecoxib, sulindac, piroxicam, indomethacin, etodolac, nabumetone, tolmetin, diclofenac, ketoprofen, apazone, and meloxicam.

65. (withdrawn) The method of claim 63, wherein the immunophilin is cyclosporine A.

66. (withdrawn) The method of claim 56 wherein the at least one first agent is selected from the group consisting of flavopiridol, ciclopirox, and methotrexate and the at least one second agent acts to inhibit glutamate-induced excitotoxicity and/or activated microglia-induced mitogenic stimulation.

67. (new) A method of treating age associated memory impairment (AAMI), mild cognitive impairment (MCI), Alzheimer's disease (AD), cerebrovascular dementia (CVD) and related retrogenic degenerative diseases, comprising administering a therapeutically effective amount of:

- i) at least one first agent capable of inhibiting neuronal cell cycle progression;
- ii) at least one different second agent capable of inhibiting activated microglial-induced mitogenic stimulation, wherein the at least one different second agent is an anti-inflammatory agent selected from the group consisting of a non-steroidal anti-inflammatory agent (NSAID), a salicylate, a steroid and an immunophilin; and
- iii) at least one third agent capable of inhibiting glutamate-induced cytotoxicity.

68. (new) The method of claim 67, wherein the at least one first agent capable of inhibiting neuronal cell cycle progression is selected from the group consisting of minocycline, any tetracycline capable of crossing the blood brain barrier, flavopiridol, ciclopirox, a paulone, indirubin, olomoucine, roscovitine, Aragusterol A, N-(3-chloro-7-indolyl)-1,4-benzenedisulfamide, and a farnesyl transferase inhibitor such as R115777, SCH66336 or BMS-214662; and wherein the at least one different second agent capable of inhibiting activated microglial-induced mitogenic stimulation is an NSAID selected from the group consisting of ibuprofen, naproxen, celecoxib, rofecoxib, sulindac,

piroxicam, indomethacin, etodolac, nabumetone, tolmetin, diclofenac, ketoprofen, apazone, and meloxicam, or a glucocorticoid, or an immunophillin selected from the group consisting of cyclosporine A and tacrolimus; and wherein the at least one third agent capable of inhibiting glutamate-induced cytotoxicity is selected from the group consisting of memantine, neramexane, amantadine, riluzole, MK801, ketamine, dextromethorphan, dextrorphan, phencyclidine, and dexanabinol (HU-211).

69. (new) A method of treating age associated memory impairment (AAMI), mild cognitive impairment (MCI), and cerebrovascular dementia (CVD), comprising administering a therapeutically effective amount of:

- i) at least one first agent capable of inhibiting neuronal cell cycle progression;
- ii) at least one different second agent capable of inhibiting activated microglial-induced mitogenic stimulation, wherein the at least one different second agent is an anti-inflammatory agent selected from the group consisting of a non-steroidal anti-inflammatory agent (NSAID), a salicylate, a steroid and an immunophillin;; and
- iii) at least one third agent capable of inhibiting glutamate-induced cytotoxicity.

70. (new) A method of treating age associated memory impairment (AAMI), mild cognitive impairment (MCI), and cerebrovascular dementia (CVD), comprising administering a therapeutically effective amount of:

- i) at least one first agent capable of inhibiting neuronal cell cycle progression; wherein the at least one first agent is selected from the group consisting of minocycline, any tetracycline capable of crossing the blood brain barrier, flavopiridol, ciclopirox, sirolimus, any sirolimus capable of inhibiting cell cycle progression, a paulone, indirubin, fascaplycin, olomoucine, roscovitine, Aragusterol A, valproate, N-(3-chloro-7-indolyl)-1,4-benzenedisulfamide, and a farnesyl transferase inhibitor such as R115777, SCH66336 or BMS-214662, and sodium butyrate;
- ii) at least one second agent capable of inhibiting activated microglial-induced mitogenic stimulation, wherein the at least one second agent is an anti-inflammatory agent selected from the group consisting of a non-steroidal anti-inflammatory agent (NSAID), a salicylate, a steroid and an immunophillin; and wherein the NSAID is

selected from the group consisting of ibuprofen, naproxen, celecoxib, rofecoxib, sulindac, piroxicam, indomethacin, etodolac, nabumetone, tolmetin, diclofenac, ketoprofen, apazone, and meloxicam; and wherein the steroid is a glucocorticoid; and wherein the immunophillin is selected from the group consisting of cyclosporine A and tacrolimus; and

iii) at least one third agent capable of inhibiting glutamate-induced cytotoxicity; wherein the at least one third agent capable of inhibiting glutamate-induced cytotoxicity is selected from the group consisting of memantine, neramexane, amantadine, riluzole, MK801, ketamine, dextromethorphan, dextrorphan, phencyclidine, and dexanabinol (HU-211).